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Antibacterial potential of Trichoderma bioactive metabolites in managing *Staphylococcus aureus* infection: Integrated molecular modeling approaches

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ABSTRACT

Staphylococcus aureus is a primary hospital-acquired infection-causing bacteria that is becoming resistant to many antibiotics. Its infection sites range from skin to soft tissue. The development of drugs for managing *Staphylococcus aureus* infection is urgently required. Targeting the enzymes involved in bacteria maintaining the integrity of cell walls could provide advances compared to other targets. Integrating molecular modeling approaches with drug-likeness properties identified the metabolites with affinity and safety to use. Molecular docking results showed that three metabolites with promising binding affinities to FmtA and interactions with the vital amino acid residues are essential in catalytic activity. The drug likeliness analysis showed that selected metabolites do not have any violations of Lipinski rules. A molecular dynamics simulation study revealed that metabolites, bisorbibutenolide and Koninginin A, exhibited the most stable complexes with FmtA. Bisorbibutenolide and Koninginin A also formed hydrogen bonds with FmtA throughout the simulation. These findings suggest that bisorbibutenolide and Koninginin A have the potential for further development as an anti-*Staphylococcus aureus* agent via targeting FmtA. Moreover, comprehensive experimental studies are necessary to validate these computational findings.

1. Introduction

Multidrug resistance (MDR) is a severe concern for the healthy life span of humans. 4.95 million people died due to MDR infections in 2019, and it can hurt more in terms of the financial burden and may claim more lives in 2050 (Murray et al., 2022). A group of bacteria (ESKAPE), including *Enterococcus faecium* (*E. faecium*), *Staphylococcus aureus* (*S. aureus*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Acinetobacter baumannii* (*A. baumannii*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Enterobacter species* (*E. species*), poses significant risks as they are major contributors to hospital-acquired infections globally. *S. aureus* is a member of the ESKAPE bacteria class, the leading cause of death due to MDR infections (Hiramatsu et al., 2014; Sonola et al., 2021). *S. aureus* is a spherically-shaped gram positive bacteria commonly found living on our skin and inside the upper respiratory tract. The 2022 National Bacterial Drug Resistance Surveillance Report found that among the 2000 hospitals monitored, *S. aureus* was the most prevalent pathogen, representing 32.3 % of clinical isolates among gram-positive bacteria (Chen et al., 2025). It belongs to a group of bacteria called Bacillota and is a natural part of our body's microbiome. *S. aureus* causes various diseases, including soft tissue and skin infections, such as endocarditis, bacteremia, osteomyelitis, and lethal pneumonia (Guo et al., 2020).

Over time, scientists have attempted to develop the Drug against *S. aureus*. Several studies have been conducted on managing *S. aureus* infections by inhibiting various mechanisms, such as cell membrane synthesis, critical enzyme participation in vital pathways, and bacteria dysfunction, by applying different classes of antibiotics (Cheung et al., 2021; Xu et al., 2008). The inhibition of essential bacterial survival mechanisms could significantly impact the management of *S. aureus* infection (Foster, 2017). Enzymes are appealing targets for drug development due to their well-defined substrate-binding pockets, which can be utilized as strategic binding sites for inhibitors (Rufer, 2021). Eliminating the active form of enzymes involved in cell wall synthesis and maintaining integrity are potentially vital targets for managing *S. aureus*

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infection. Teichoic acid is an integral part of gram-positive bacteria and an essential cell wall component (Swoboda et al., 2010). Teichoic acid stimulates the bacterial cell wall membrane in the presence of these FmtA enzymes (Rahman et al., 2016). FmtA belongs to the esterase class of enzymes that perform dual functions, such as cell wall synthesis and autolysis, to promote bacterial growth and development (Qamar and Golemi-Kotra, 2012). FmtA contains conserved motifs characteristic of serine active-site penicillin-binding proteins (PBPs), β-lactamases, and a conserved catalytic triad accompanied by Ser-Lys-Asp (Dalal et al., 2019; Uddin et al., 2023). Genome-associated studies showed that the FmtA mutated form reduces the MICs of antibiotics that target cell wall synthesis (Zhao et al., 2012).

Naturally derived metabolites have been known to treat human disease for a long time. Several FDA-approved drugs are derived from natural products, and the sources of these drugs are bacteria, fungi, and plants (Patridge et al., 2016). This study use *in silico* approaches, including molecular docking, molecular dynamics simulations, and MMPBSA calculations to evaluate the binding affinities of Trichoderma-derived metabolites with FmtA. Trichoderma, known as the biopesticides activities, and its metabolites showed a higher affinity against enzymes of plant disease-causing organisms (Singh et al., 2022a, 2022b). The affinity of Trichoderma metabolites at the active site of Fmt A enzyme was evaluated by combining the following approaches: Molecular Docking, Molecular Dynamics Simulation, and MMPBSA.

2. Methodology

2.1. Selection of metabolites and toxicity analysis

The metabolites library of Trichoderma species was prepared based on the literature and metabolites information presented in Table S1 (Reino et al., 2007). The metabolite's information, such as canonical smiles, CID numbers, 3D structures, and IUPAC names, were retrieved from the PubChem database (Kim et al., 2023). The toxicity analysis of these Trichoderma bioactive metabolites was performed using the Pro-Tox server II (Banerjee et al., 2018). Metabolites with higher LD50 and toxicity scale at 6 were considered for molecular docking (Table S2). The selections of higher LD50 correlated with lower toxicity while exposure to the human body (Gadaleta et al., 2019). Toxicity is essential for the initial screening of drugs for safe treatment, and determination of toxicity at the preclinical stages enhances the cost of the drug development process (Guengerich, 2011).

2.2. Molecular docking

2.2.1. Preparation of the receptor

The 3D coordinates of the FmtA enzyme were obtained from Protein Data Bank (PDB) with PDB id 5ZH8 (resolution: 2.58 Å) (https://www.rcsb.org/structure/5ZH8). Preliganted non-protein moieties such as ions and water were removed. A single chain was retained, and a clean geometry module built-in Discovery Studio v4.0 (San Diego, CA, USA) was applied to retain conformational fate. The corrected protein was then saved in PDB format. This optimized PDB file was subsequently processed using MGL v1.5.6 to prepare it for molecular docking (https://www.scripps.edu/La Jolla, CA). MGL Tools assists in adding hygrogen atoms and Kollman charges (−1.642) and saves them into PDBQT format.

2.2.2. Preparation of Trichoderma ligand

3D coordinates of ligands were retrieved from the PubChem database (Kim et al., 2023). The 3D coordinates of ligands were further processed for docking purposes. The Universal force field and the steepest descent approach for 200 were applied for energy minimization for ligand processing, further saved in a pdbqt file with an energy convergence threshold of 0.1 kcal/mol. The ligand processing was done using open babel tools built in PyRx v0.8 (https://openbabel.org/; https://pyrx.sourceforge.io/).

2.2.3. Molecular docking of Trichoderma metabolites and FmtA

Molecular docking has been used to calculate the binding affinity and interaction of interacting molecules. The molecular docking was performed using Autodock Vina v1.1.2 (https://www.scripps.edu/La Jolla, CA). Molecular docking was performed at the amino acid residues of the active site by applying the grid box. The grid box was assigned to the amino acid residues of active site amino such as Ser127, Lys130, and Asp213 (Dalal et al., 2019). The grid parameters, such as grid dimension, were set as X = 7.075 Å, Y = 43.439 Å, and Z = 3.921 Å, and grid size was done at X = 18 Å, Y = 18 Å, and Z = 18 Å with the spacing 1 Å. The docking was run by setting exhaustiveness values 16. The 2D interaction of FmtA and metabolites was visualized via Discovery Studio v4.0 (San Diego, CA, USA).

2.3. Drug likeness of selected metabolites

The properties of pharmacokinetics and pharmacodynamics are essential for whether a molecule can enter the human body and perform the desired biological activity. The Druglikeness parameter was evaluated using the SWISS-ADME (Waterhouse et al., 2018). The canonical smiles were used as input data.

2.4. Molecular dynamics simulation (MD simulation)

MD simulation investigated the structure in addition to stability for the complexes formed between FmtA and Trichoderma metabolites in water and physiological salt concentration using GROMACS v2018. The details of the simulation setup were covered in previous publications (Arora et al., 2024). The data was compared with the apo form of FmtA. The production run of the MD simulation was for 100 ns to find the conformational stability and interactions of the complexes. Furthermore, the FEL (free energy landscape) of FmtA unbound and ligand-bound bound states were also analyzed (Choudhir et al., 2024).

2.5. Molecular Mechanics Poisson–Boltzmann Surface Area (MMPBSA)

MMPBSA is a popular method to predict the binding affinity of interacted molecules. For the MMPBSA analysis, the last 10 ns MD trajectories were chosen to estimate the various energy parameters, including weak non-covalent interactions (e.g., van der Waals and polar solvation), SASA, and the binding force among the interacting molecules. This method simulates the energy changes involved in the recognition process between the interacting metabolites (Kumari et al., 2014).

3. Results and discussion

3.1. Molecular docking

Drug-disease target interactions and binding affinities are essential for drug design (Sadybekov and Katritch, 2023). The binding energy of disease targets and drugs assists in the selection of medicines among the groups of drugs. Computational approaches, such as molecular docking and MD simulation, assist in elucidating binding affinity and interaction of Drug and target, which can significantly reduce the drug discovery cost (Sadybekov and Katritch, 2023).

The docking results showed that the binding energy of Trichoderma metabolites and FmtA was distributed from −4.5 to −7.8 kcal/mol (Table S3). Metabolites with binding energy below −7.0 kcal/mol were chosen for interactions and binding energy analysis. Trichotetronine showed the minimum binding energy among the top three molecules. The binding energy of trichotetronine found in the docking studies was −7.8 kcal/mol. The interaction analysis showed two H-bonds formed between the trichotetronine and protein residues (Ser-127 and Gly-345).

Amino acid residues such as Lys130, Lys179, Asp213, Tyr334, and Gly344 were involved in the van der Waals interactions. Amino acid residues showed that amino acid residues such as His173, Tyr211, Tyr282, Tyr329, Phe346, and Phe347 interact through the Pi-alkyl interactions (Fig. 1 B). The binding affinity of bisorbibutenolide was found to be −7.7 kcal/mol. The interaction results showed that amino acid residues Ser127 and Lys179 form H-bonds with bisorbibutenolide. Protein residues such as Lys130, Tyr211, Asn212, Asp213, Tyr329, Leu342, Asn343, Gly344, Gly345, and Lys268 interact with bisorbibutenolide using van der Waals. Pi-alkyl interactions also formed between the bisorbibutenolide and amino acid residues such as Tyr282, Tyr334, Phe346, and Phe347 (Fig. 1 C). Koninginin A had a binding affinity of −7.0 kcal/mol. Three H-bonds formed between koninginin A and residues such as Ser127 via two H-bonds, and Asn212 formed a single hydrogen bond. Amino acid residues such as Lys179, Asp213, Tyr334, Gly344, and Phe347 interacted using van der Waals interactions. Amino acid residues such as His173, Tyr211, Tyr282, and Phe346 interacted using Pi-alkyl interactions (Fig. 1 D). The analysis of binding energy and interactions showed that trichotetronine, bisorbibutenolide, and koninginin A have significantly lower binding energies. All three selected metabolites interact with the critical catalytic residues, including Ser127, Lys130, Tyr 211, and Asp213 (Fig. 1B, C, and D). The surface diagram and all three interacting metabolites showed that all the metabolites bind in similar pockets (Fig. 1A).Previous studies showed that trichotetronine, bisorbibutenolide, and Koninginin A reported biological activities such as antifungal, antioxidant, and anticancer, respectively (Ngo et al., 2021; Ramos et al., 2024; Washida et al., 2007). Further, drug-likeness and MDS were performed to assess the Drug's safety and binding stability in physiological conditions.

3.2. Drug likeness of selected Trichoderma metabolites

The druglike properties are an essential parameter to reduce rejection of the Drug in later stages. These parameters provide insights into how drugs and the human body respond to each other. The drug-like properties results indicate that selected metabolites have zero violation in Lipinski rules. Koninginin A has no violation for Lead-likeness, whereas Trichotetronine and Bisorbibutenolide have a single violation for Lead-likeness (Table 1). The lead likeness and drug-likeness parameters can provide the advantage of modifying these metabolites for the desired biological activities.

3.3. Molecular dynamics simulation (MDS)

Molecular dynamics simulation is a computer-based technique where we try to assess the motion of atoms in physiological conditions such as water, salt, and other parameters (Durrant and McCammon, 2011). MD Simulation assesses the stability and interactions concerning various parameters during the molecular simulation time.

3.3.1. Root mean square deviation (RMSD) analysis

RMSD tracks the complexes' stability during the simulation. Oscillation in RMSD values correlated with the firmness of protein and interacting entities in a simulation (Aier et al., 2016). The backbone RMSD analysis showed that RMSD lies in the 0.2–0.3 nm range. Backbone RMSD does not show alternation during the simulation (Fig. 2A).

Table 1
Druglike properties of selected Trichoderma Metabolites.

Properties	Trichotetronine	Bisorbibutenolide	Koninginin A
Molecular weight (g/mol)	496.55	496.55	284.39
Lipinski Violation	0	0	0
TPSA (Å^2)	138.20	138.20	58.92
Leadlikeness violation	1	1	0
Synthetic accessibility	6.75	6.75	6

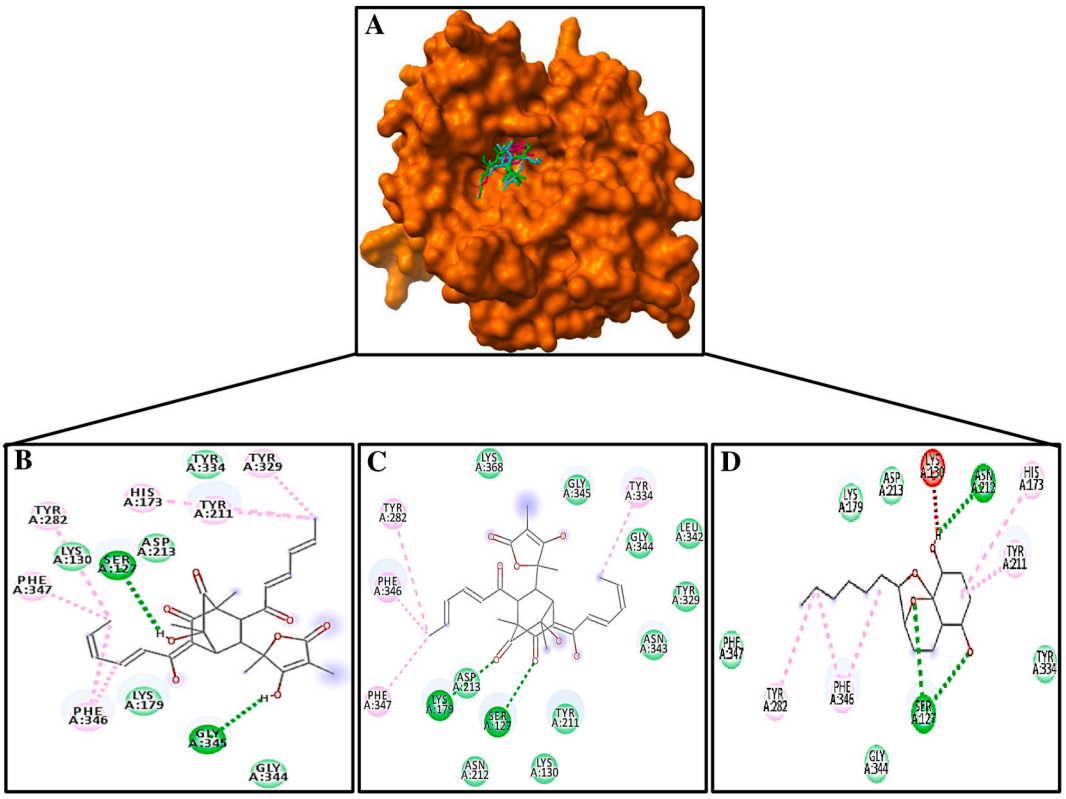

Fig. 1. Interactions of Fmt A and docked molecules (A) Surface diagram of all three top molecules and Fmt A (B) Trichotetronine, (C) Bisorbibutenolide, and (D) Koninginin A.

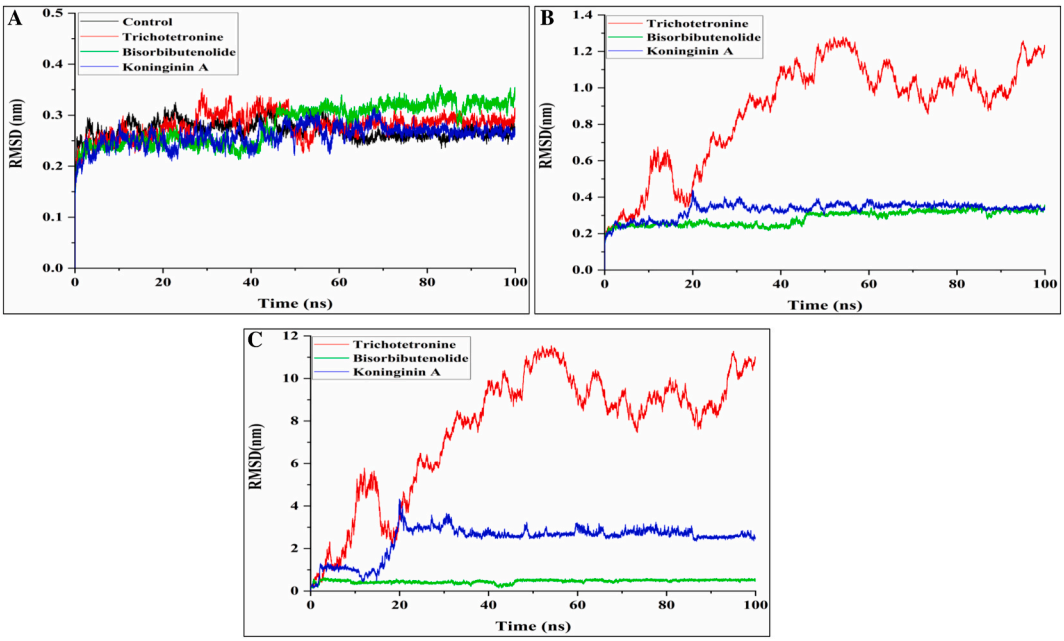

Fig. 2. Stability analysis of GSK-1 during the simulation time (A) Backbone RMSD (B) complex RMSD (C) ligand RMSD.

The complex RMSD analysis showed that bisorbibutenolide had higher stability than koninginin A, followed by trichotetronine (Fig. 2B). Tricotetronine was completely expelled during the simulation. Ligand RMSD also showed similar trends during the simulation (Fig. 2 C).

3.3.2. *Root mean square fluctuations (RMSF) analysis*

RMSF exhibited the flexibility of amino acid residues during the simulation. The higher values of RMSF convey that macromolecules are flexible compared to residues with less RMSF (Zhu et al., 2022). The deviation in the RMSF values during the simulation time can be used to assess the variations in amino acid residue flexibility. The RMSF analysis showed that N-terminal amino acids had higher fluctuations than amino acids present in the core regions in proteins. Other than terminal amino acid residues, most amino acid residues showed fluctuations of around 0.2 nm (Fig. 3). The RMSF results showed that the binding of Trichoderma metabolites does not appear to be a deviation in the RMSF values in the bound and unbound states.

3.3.3. *Radius of gyration (Rg) analysis*

The radius of Gyration is a measure of macromolecules' compactness that reveals how densely macromolecules packed during the adaptation of structural integrity. The structural parameters such as alpha-helix, beta-sheet, and coiled regions also play vital roles in the Rg parameters of proteins (Funari et al., 2022). The variation in Rg values indicates the conformation integrity of proteins by drug binding or other molecules. Higher values of Rg correlated to a reduction in the compactness of proteins. The Rg analysis showed that all four systems showed compactness in the 2.0–2.05 nm (Fig. 4). The binding of metabolites does not lose force to the FmtA to lose its structural integrity.

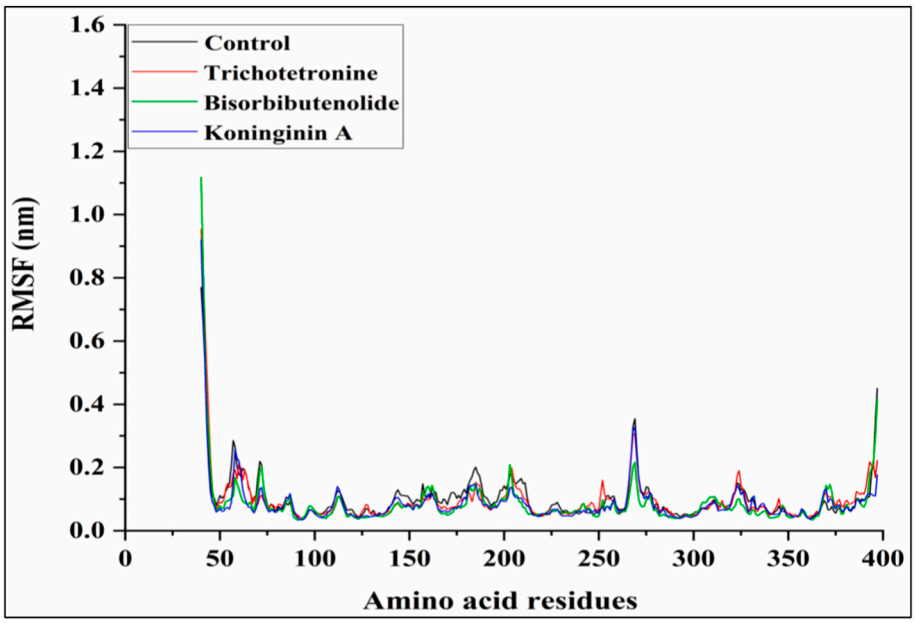

Fig. 3. Amino acid residue-wise fluctuations (RMSF) of bound and un-bound state of FmtA.

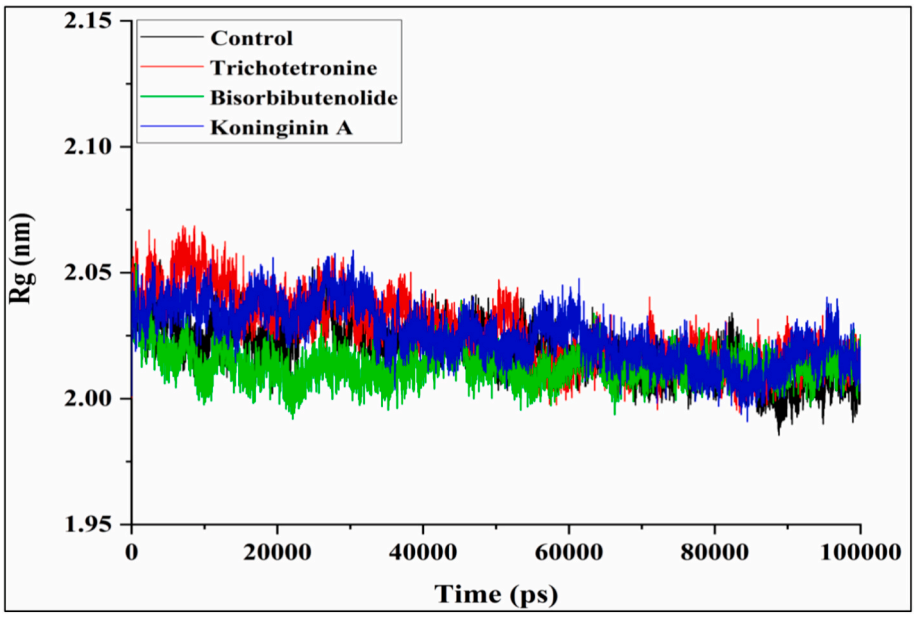

Fig. 4. (A) Radius of gyration analysis of Fmt An unbound and Bound State.

3.3.4. *Solvent-accessible surface area (SASA) analysis*

Solvent Accessibility (SASA) is a crucial property of proteins that significantly influences their folding, stability, and interactions with other molecules (Savojardo et al., 2021). Proteins are susceptible to their environments. SASA gives insights into the exposed area of a protein surface to its surrounding metabolites via the modulation of their structural and functional properties. The protein's folding properties are often affected by ligand binding; sometimes, it is exposed or forced to be buried. The SASA analysis showed that the initial stages before 30000 ps SASA were distributed in the 165–195 nm^2 range. After the 30000 ps simulation, SASA values were reduced by 165–185 nm^2, meaning proteins became buried with the simulation time (Fig. 5). The binding of metabolites does not show a significant difference in SASA values compared to unbound FmtA.

3.3.5. *Hydrogen bond analysis*

The formation of hydrogen bonding is critical for the interactions between protein and Drug in simulation. The hydrogen analysis showed the hydrogen bond formed during the 100,000 ps simulation. The bisorbibutenolide has maximum hydrogen bonds compared to koninginin A, followed by trichotetronine (Fig. 6 A). Hydrogen bond distribution analysis manifested that the bisorbibutenolide has a higher bond distribution among the selected metabolites (Fig. 6 B).

3.3.6. *Eigenvector and free energy landscape (FEL)*

Covariance matrix analysis suggests minimal variations between the systems' eigenvector values, indicating that metabolites binding doesn't significantly affect protein structural stability (Fig. 7). Free energy analysis showed that the apo and metabolites bound forms of FmtA do not significantly differ in free energy. Further free energy landscape analysis reveals that FmtA in the apo-form possesses three energy

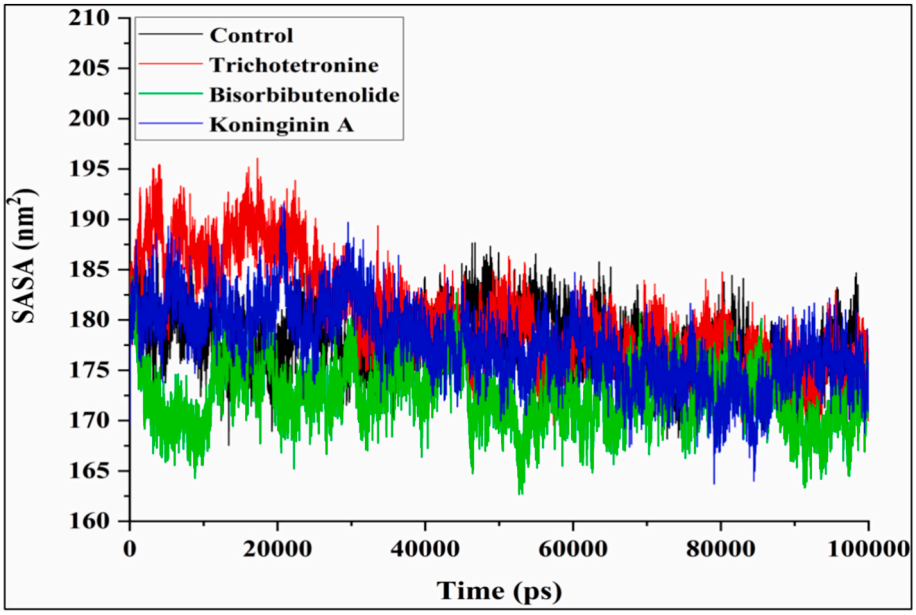

Fig. 5. Solvent Accessible Surface Area of Fmt An unbound and Bound State during the simulation.

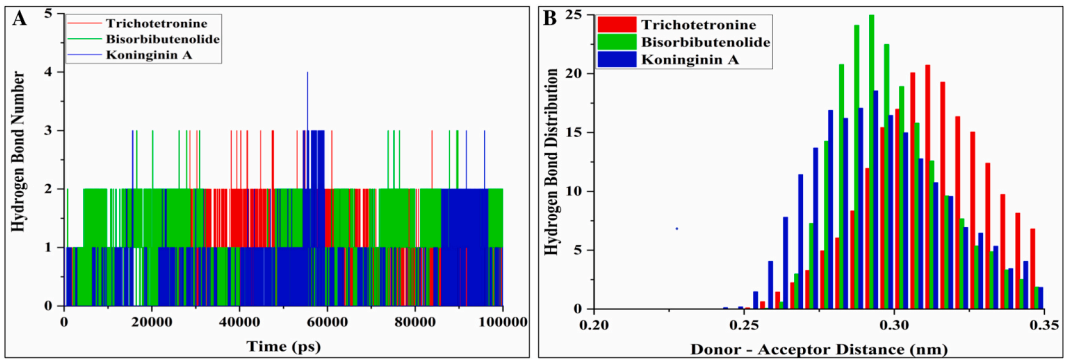

Fig. 6. Hydrogen bond analysis (A) Hydrogen bond formed (B) hydrogen bond distribution during the simulation time.

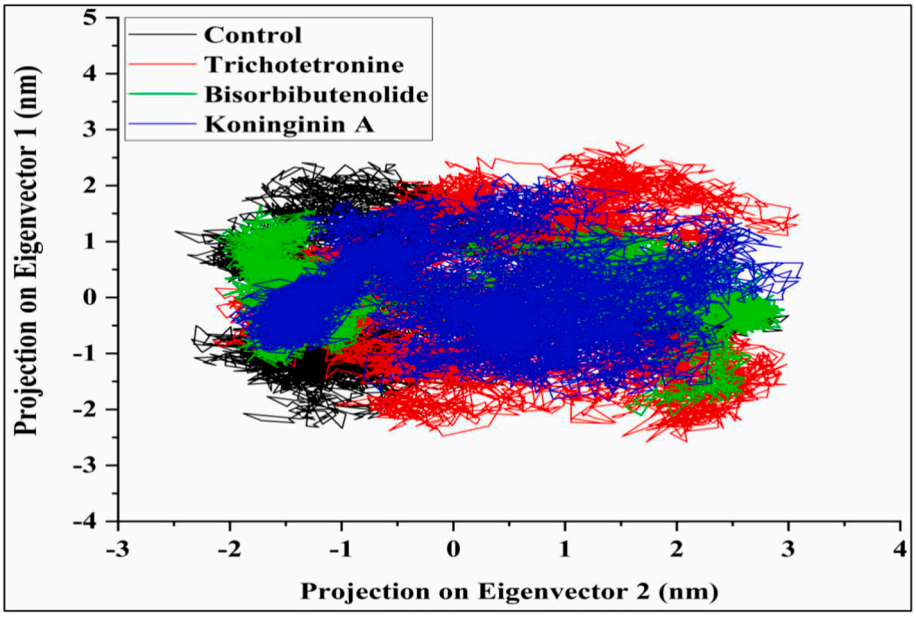

Fig. 7. Eigenvector analysis of Apo form of Fmt A and ligand-bound state.

minima (8A). This number showed the perturbation upon metabolite binding (Fig. 8B). In the case of the trichotetronine-bound state, FmtA exhibits a single energy minimum (Fig. 8C), while the bisorbibutenolide-bound state shows four minima, one with a larger size and the remaining three occupying a considerably smaller space (Fig. 8D). The koninginin A-bound FmtA displays two energy minima, one large and one small. The FEL analysis revealed that the binding of structurally diverse metabolites slightly impacts FmtA ′s structure.

3.4. Molecular mechanics Poisson-Boltzmann surface area analysis

MMPBSA has been frequently used to predict the binding between the protein and ligand complexes in the aqueous environment (Wong et al., 2009). The MMPBSA analysis predicted binding energy using the vacuum's polar, non-polar, and potential energy in the vacuum. The koninginin A and bisorbibutenolide showed binding energy −64.17 ± 19.00 and −44.53 ± 15.12 kJ/mol, respectively. However, Trichotetronine showed a binding energy positive 33.51 ± 24.20 kJ/mol. Thus, trichotetronine has less affinity with FmtA than the other two ligands considered in the study. Table 2 provides details of the different MMPBSA energy values.

4. Discussion

Inhibition of critical enzymes involves various pathways essential for bacterial survival and can be mighty in managing bacterial infections (Güller et al., 2021). FmtA constitutes a crucial enzyme that involves methicillin resistance of *S. aureus* because it maintains cell wall integrity. The functions of the conserved active site residues differ as follows: Tyr retains the incoming substrate, at the same time, WTA is hydrolyzed, Lys performs acylation or deacylation, and Ser behaves as a nucleophile (Qamar and Golemi-Kotra, 2012). FmtA has been shown to have an esterase activity that removes D-alanine, which constitutes teichoic acids. This esterase activity is connected to the modulation of charges on teichoic acid and, as a result, may be linked to the self-lysis, invasion, and growth of *S. aureus* (Rahman et al., 2016). Numerous antibiotic families that belong to beta-lactams and naturally occurring metabolites have been examined over time to block the activity of FmtA and alleviate *S. aureus* infections namely Vancomycin, Fosfomycin, Daptomycin, Teichoic Acid Inhibitors, and Phage Therapy (Coupri et al., 2021; Ishaq et al., 2021; Ji et al., 2020; Nguyen et al., 2024; Ruan et al., 2020; Zhou et al., 2023; Zhu et al., 2022). Although many antibiotics and natural compounds have been studied to inhibit the enzyme FmtA, each has inherent drawbacks, especially concerning bioavailability and the emergence of resistance. Hence, developing novel antibacterial substances is essential to counteract *S. aureus* resistance among 15

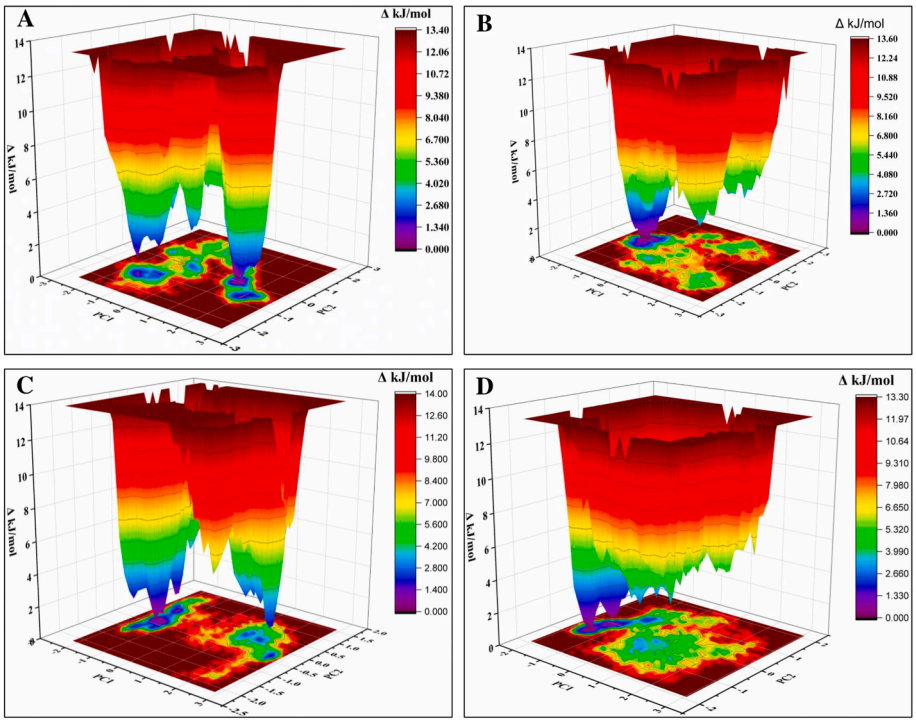

Fig. 8. Gibbs free energy profiling of (A) Apo form of Fmt A, (B) trichotetronine, (C) bisorbibutenolide, and (D) koninginin A.

Table 2
Binding free energy of FmtA and metabolites complexes using MMPBSA.

Energy (kJ/mol)	Trichotetronine	Bisorbibutenolide	Koninginin A
Van der Waal energy	−0.00 ± 0.00	−162.99 ± 12.14	−85.50 ± 11.01
Electrostatic Energy	−2.70 ± 0.61	−61.15 ± 13.39	−19.12 ± 8.32
Polar Solvation Energy	36.24 ± 24.29	199.82 ± 22.29	51.23 ± 16.69
SASA Energy	−0.019 ± 1.30	−20.21 ± 0.99	−10.79 ± 0.98
Binding Energy	33.51 ± 24.20	−44.53 ± 15.12	−64.17 ± 19.00

compounds, Trichotetronine, Bisorbibutenolide, and Koninginin A, with a higher affinity with the FmtA enzyme based on docking results.

Further MDS studies showed that Koninginin A and bisorbibutenolide showed stable complexes, whereas trichotetronine showed loose binding. Throughout the simulation, bisorbibutenolide, in particular, formed numerous hydrogen bonds and maintained constant interaction dynamics, making it the most stable inhibitor. Integrating molecular docking, MDS, and MMPBSA results showed the possibility of becoming an anti-*S. aureus* drug via targeting FmtA. Additionally, trichotetronine does not have a favorable MMPBSA binding energy due to the lack of tight binding, as shown in Table 2. Drug favorable and target interaction depend on binding energy and other parameters such as RMSD, RMSF, Rg, and SASA (Wu et al., 2024). The comprehensive analysis of results showed that Bisorbibutenolide and Koninginin A may be used as the FmtA inhibitors and possibly for treating *S. aureus* infections. The Trichoderma metabolites have been reported to have a higher affinity with enzymes related to plant pathogens (Singh et al., 2022a, 2022b).

5. Conclusion

The binding affinities and interactions between Trichoderma metabolites and FmtA were analyzed using *in silico* approaches, including molecular docking, molecular dynamics (MD) simulations, and Molecular Mechanics Poisson–Boltzmann Surface Area (MMPBSA) calculations. Among the tested compounds, bisorbibutenolide and koninginin A exhibited strong binding affinities and enhanced stability with FmtA, suggesting their potential as promising candidates for anti-*Staphylococcus aureus* therapy. However, before considering bisorbibutenolide and koninginin A as viable antimicrobial agents, further validation through in vitro and in vivo studies is essential to confirm their efficacy and safety.

CRediT authorship contribution statement

Gourav Choudhir: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Israil:** Writing – review & editing, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Faiza Iram:** Writing – review & editing, Visualization, Formal analysis, Data curation. **Mohammad Shahid:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition. **Anas Shamsi:** Writing – original draft, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Md. Imtaiyaz Hassan:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Asimul Islam:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors state that they have no conflicts of interest, such as financial gains or personal connections, that could have potentially biased their research findings.

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Appendix A. Supplementary data

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